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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,625	KUFER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *3,5,8-18,24,25 and 27-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 8-18, 24, 25, 27-41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Further, claims 3, and 5 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

This application contains claims 3, 5, 8-18, 24, 25, and 27-41, drawn to an invention nonelected. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-41 are pending. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections, Withdrawn

The objection of the claims is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

Rejection of claims 2, 4, 6, 7, 19, 20, 21, 22, 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment in claims 2, 4, 6, 7, 19, 21-22, and the persuasive argument for claim 20.

Claim 26 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant states that the rejected limitation "limited" would be amended in the Remark section but the claim is not amended yet.

Claim Rejections - 35 USC § 102, Maintained

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Muller et al., (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) as evidenced by WO 97/01580 (a copy provided with ISR).

The claims are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the heterodimer is not formed by interaction between the two polypeptides but formed by CH1 domain and CL domain, wherein said two polypeptides bind different receptors or have different ligand functions (claim **1**), wherein claim **2** describes how the two polypeptides are linked to either said CH1 domain or said CL1 domain i.e., C-and/or-N-terminal, wherein claim **4** further limits said heterodimer to have four functional domains, wherein claim **6** further limits at least one of the two polypeptides to be a scFv-fragment, wherein claim **7** further limits at least one of the two polypeptides to have an antigen binding region specific for a tumor associated antigen, wherein claim **19** further limits said CL1 domain to be from kappa

chain of an immunoglobulin, wherein claims 20-22 further limit how said CH1 domain or said CL domain is connected to the different polypeptides, namely by a polypeptide linker (claim **20**), an Ig-hinge region (claim **21**), or an IgG hinge region (claim **22**), wherein claim **26** further limits said CH1 domain be linked to a histidine tag.

Applicant argues that claim 1 as amended recites a multifunctional compound comprising functional domains having different receptor or ligand functions, wherein further at least two of said different functional domains lack an intrinsic affinity for one another. In contrast, Muller et al. disclose bispecific antibodies having two different scFv-fragments. In the specification, it was noted that the results of Mûller et al. using C1 and CHI to support dimerization of scFv fragments is not surprising because scFv-fragments are also known to form dimers with each other even without the support of any special dimerization domains (specification as filed, page 7, lines 24-26). That is, scFv-fragments are a class of molecules well documented in the literature as forming dimers due to mutual affinity, even without the support of a dimerization domain. Accordingly, the bispecific antibodies disclosed by Mûller et al. are not the claimed multifunctional compounds comprising functional domains having different receptor or ligand functions, wherein further at least two of said different functional domains lack an intrinsic affinity for one another. Applicants present the following support for the argument that the bispecific antibodies containing scFv fragments disclosed in Muller et al. al. are not the claimed multifunctional compounds. Applicant cites Kortt et al., and Griffith et al., to support that scFv fragments can form dimers. Applicant concludes that Muller el al., do not disclose a multifunctional compound comprising functional domains

having different having different receptor or ligand functions, "wherein further at least two of said different functional domains lack an intrinsic affinity for one another". These arguments have been fully considered but found unpersuasive for following reasons.

In contrary to applicant's assertion that the multifunctional compound of Muller et al., do not have at least two of said different functional domains lack an intrinsic affinity for one another, the disclosed protein complex of Muller et al. (see the pictorial illustration shown in Fig. 1A) has at least two of the different functional domains (i.e. antiEGR-R and anti-CD2) lack an intrinsic affinity for one another. Note antiEGR-R and anti-CD2 are not attached to each other. The two polypeptide chains of Muller et al., is is linked via immunoglobulin constant chains (i.e. CH1 and CL), which is identical to the multifunctional compound as claimed in instant claim 1.

As stated before in the previous Office actions, Muller et al., teach a heterodimer comprising two monomers, wherein the first monomer comprises CH1 domain linked via C-and/or-N-terminal to two functional domains i.e. VH and VL functional domains of anti-EGF-R scFv fragment, and the second monomer comprises CL1 linked via C-and/or-N-terminal to two other functional domains i.e. VH and VL functional domains of anti-CD2 scFv fragment (total four functional domains in the multifunctional compound, as specified instant claim 4), wherein the two different polypeptides (i.e. anti-EGF-R scFv fragment and anti-CD2 scFv fragment) lack an intrinsic affinity for one another, wherein the heterodimer is formed by a disulfide bond between the CH1 domain of the first monomer and the CL domain of the second monomer (note Fig.1, the heading "Materials and methods" at pages 259-261, and Fig. 2), wherein at least one of the two

monomers is to be able to bind a tumor associated antigen (note page 259, right column, 1st paragraph, where it teaches "miniantibodies capable of binding to the EGR receptor" that is "overexpressed by a wide range of tumors"), wherein said CL1 domain is from the kappa type chain of an immunoglobulin (note line 8 under the sub-heading "plasmid construction" at page 259, left column), wherein the CH1 domain or the CL domain is connected to the different four functional domains, at least two of the four functional domains having a ligand function to a EGF receptor (note page 259, 1st paragraph), namely by a polypeptide linker, or an Ig-hinge region, more specifically an IgG hinge region (note line 8 under the sub-heading "plasmid construction" at page 259, left column and Fig. 1B), wherein the CH1 domain is linked to a histidine tag (note line 2 from bottom of page 259, left column under the sub-heading "plasmid construction" and Fig. 1B).

The recitation of "produceable in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains" in claim 1 does not appear to limit either the function and/or structure of the claimed multifunctional compound. In other words, the instant claim 1 appears to say that the claimed multifunctional compound **can be** produced "in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains". WO 97/01580 is cite to demonstrate that a multifunctional compound can be produced in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains before the effective filing date of the instant application. 97/01580 at page 16 especially lines 16 "a mammalian" host cell can be use to produce an engineered fully functional heterodimer antibody, and also

teach at page 18 especially lines 4-20 a secretion signal that could be used in a mammalian expression system. Thus, the claimed multifunctional compound could be producible in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains. The Office emphasizes that WO 97/01580 is not cited to explain the structural limitation of the claimed multifunctional compound.

If the limitation "produceable in a mammalian host cell as a secretable and fully functional heterodimer of two polypeptide chains" in claim 1 is intended to specify how the claimed product is made, then the reference does not describe the production of the heterodimer using the method identical to that is recited in claim 1. However, the recitation of a process limitation in claim 1 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 1 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed product and the product of the reference.

The method in which the heterodimer is produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process in a claim is the same from the product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al., (30 January 1998, a copy provided with ISR, FEBS Letters, vol. 422, pages 259-264) in view of Pluckthun and Pack (1997, Immunotechnology, vol. 3, pages 83-105).

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 are interpreted as drawn to a heterodimer i.e. a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide, wherein the linking is done by the **upper hinge region of human IgG3** (claim **23**). See the interpretation of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 above for further details.

Applicant argues that Muller et al., do not teach all of the limitation of claims for the reasons given traversing 102 (b) rejection above. However, Muller et al., stand as an 102 (b) art for the reasons given above.

As stated above in the rejection of 102(b), and also in the previous Office action, Muller et al., teach a multifunctional compound comprising two monomers, wherein the first monomer comprises CH1 domain linked to a polypeptide, and the second monomer comprises CL1 linked to a different polypeptide with all the structural limitations of claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26. Muller et al., at the last sentence under the heading "Introduction" also teach why one of ordinary skill would be motivated to use a human sequence i.e. to reduce immunogenicity in a human subject.

Muller et al., do not specifically teach "the upper hinge region of human IgG3".

However, Pluckthun and Pack teach at page 89, left column, 1st paragraph "the use of hinge regions creates a spacing, hinge bending and rotational freedom of the associated scFv fragments, similar to the Fv-arms of a complete antibody...but with a fraction of its molecular weight. This was achieved by not adding the dimerization handle directly to the scFv fragment, but rather separated **by the upper hinge** from murine or **human Ig3**, known to lead to a flexible arrangements of domains". Further, Pluckthun and Pack teach at the paragraph bridging pages 95-96 that a human IgG hinge region has been used for therapeutic application, which requires reduced "immunogenicity" in a human clinical application.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute the linkers of Muller et al., with the upper hinge region of human IgG3 taught by Pluckthun and Pack, to make a multifunctional compound. This would have been accomplished with a reasonable expectation of success since combination of Muller et al., (Jan. 1998) and Pluckthun and Pack (1997) teach how to make each elements of the claimed invention. One of ordinary skill in the art would have been motivated to make and use the claimed multifunctional compound using the upper hinge region of human IgG3 as the linker because Pluckthun and Pack teach that the upper hinge region of human IgG3 is good for reducing immunogenicity in a human patient and the human IgG3 is also good for its flexibility.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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